**Malaria is a disease of poor countries. The development of malaria vaccines requires considerable investment, for which there is little commercial interest, particularly for transmission-blocking vaccines that have the public health objective of protecting communities from the spread of malaria rather than protecting individuals from the disease. Here, Carter *et al.* summarize the report of a committee of experts on the relevance and prospects for these vaccines.**

# Malaria transmission-blocking vaccines—how can their development be supported?

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Malaria, historically one of the greatest causes of human misery and death[1–3], is today relatively contained outside of Africa. This is being achieved with insecticides to attack the mosquito vectors and by treating human infections with anti-malarial drugs. However, partly through the emergence and spread of resistance by the parasites and their vectors to these chemically based methods of control, this containment is being steadily eroded. The problem is exacerbated by concerns for the environment stemming from the use of insecticides such as DDT (refs. 4,5). Therefore, alternative approaches to malaria control are urgently needed. Malaria vaccines have long been the subject of intensive research, and although they have yet to be realized clinically, they are at least now becoming a technical possibility[6–8].

In the second part of the last century, vaccines against infectious diseases proved very effective. Successful vaccination campaigns against polio, yellow fever, small pox, measles and so on not only protected the vaccinated individuals against infection but also protected others in the community by reducing the further spread of the infection. Likewise, malaria vaccines are being developed to achieve both protection of the vaccinated individual and the reduction of malaria transmission through the community.

However, for the malaria parasite, the stages that cause disease are different from the stages that transmit the parasites from the mosquito vector to the human host and vice versa. Accordingly, vaccines are being developed against the different parasite stages to achieve these different effects (Fig. 1). Liver-stage vaccines will reduce the chance of a person becoming sick. Asexual blood-stage vaccines will reduce disease severity and risk of death during infection. Vaccines against stages that infect mosquitoes will directly prevent the spread of malaria through the community. It is this last group that are known as malaria transmission-blocking vaccines[9] (TBVs).

One of the main problems confronting malaria vaccine development in general is the relatively low level of commercial interest. This is because the potential market with endemic malaria is mainly in the poorest countries who despite their medical need, do not have the economic means to support large-scale purchase and distribution. In fact, industry's greatest interest is in liver- and blood-stage vaccines, which are being designed to target travelers and the military entering malaria-endemic regions from the wealthy and mostly malaria-free regions of the world. Unfortunately, it is proving almost impossible to stimulate commercial development of TBVs whose use would be restricted to poor, malaria-endemic countries.

TBVs prevent the transmission of malaria by inducing antibodies against antigens present on the sexual stages of the parasites, which develop in the mosquito midgut, and thus block their development in the mosquito. Candidate formulations at or approaching a grade suitable for testing as human TBVs are now available (D. Kaslow and C. Long, personal communication) (Table 1 & 2). Research-grade formulations of TBV candidates have been shown to induce antibodies that completely block transmission to mosquitoes of the two principal human malaria parasites, *P. falciparum* and *P. vivax*[9] (H. Hisaeda *et al.*, personal communication).

Although, motivated by the public health relevance of the

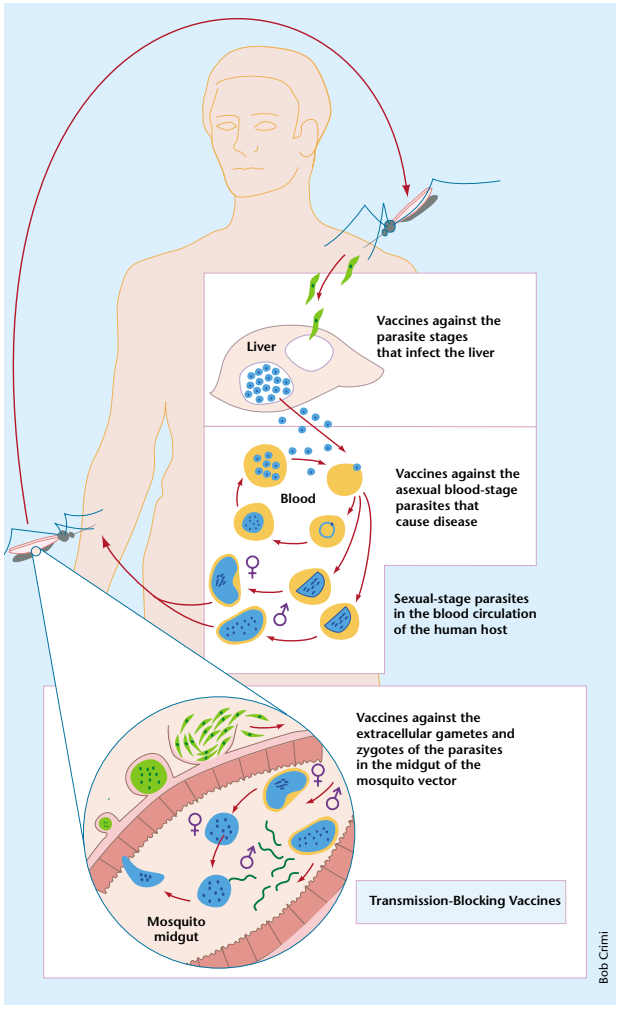


**Fig. 1** Different stages of the malaria parasite life cycle against which vaccines are being developed.

**Table 1** Properties and current state of product development of leading malaria transmission-blocking vaccine candidates

| Antigen | Strengths | Weaknesses | Current state of development |
|---|---|---|---|
| Pfs25 and Pvs25 | Antibodies against Pfs25 or Pvs25 can completely block transmission of *P. falciparum* or *P. vivax* to mosquitoes.<br><br>In most areas where TBV would be used both *P. falciparum* and *P. vivax* are endemic. Therefore, it is very important that both Pfs25 and Pvs25 are being developed to be used together in the same vaccine. | Not expressed in the human host and so not subject to natural boosting by malarial infection following vaccination.<br><br>Because immunity to these vaccines will probably not be boosted by natural infection, formulations to prolong the immune response to vaccination may need to be developed.<br><br>Parasites can still infect mosquitoes when the gene for these proteins has been knocked out. | *P. vivax* and *P. falciparum* genes both cloned and expressed.<br><br>Vaccination with both the *P.vivax* and *P. falciparum* yeast-expressed clones induces complete transmission-blocking in model systems.<br><br>Clinical grade yeast-expressed Pfs25 produced.<br><br>Clinical grade yeast-expressed Pvs25 soon to be produced. |
| Pfs28 and Pvs28 | Similar to Pfs25 and Pvs25. | Similar to Pfs25 and Pvs28. | Similar to Pfs25 and Pvs25 but clinical grade material being planned. |
| Pfs25 + Pfs28 and Pvs25 + Pvs28 | Parasites cannot infect mosquitoes if both 25 and 28 genes are knocked out. Therefore, there is advantage to combining the 25 and 28 molecules in the same vaccine because, while the parasites can evade immunity against either one by deleting its gene, they cannot survive the deletion of both genes. Immunization with both 25 and 28 may be synergistic in inducing transmission blocking antibodies. | Not expressed in the human host and so not subject to natural boosting by malarial infection following vaccination.<br><br>Because immunity to these vaccines will probably not be boosted by natural infection, formulations to prolong the immune response to vaccination may need to be developed. | See above. |

transmission-blocking effects of vaccination against malaria, the scientific community and its funders have made much progress towards the technical development of this type of malaria vaccine[9], TBV development has proceeded slowly, mainly because of the lack of a committed industrial partner. It is timely, therefore, to ask how essential TBVs would really be for malaria control, and, if they were developed, how this could be achieved.

A meeting* to discuss these issues included representatives from the pharmaceutical industry and major funding agencies, scientific experts with detailed knowledge and experience in the technical aspects of malaria vaccine development and regional representatives and experts in malaria epidemiology and in medical ethics. This meeting's purpose was to achieve an authoritative statement on the issues concerning malaria TBVs (ref. 10).

Central to the discussions was the practical value of TBV as a tool for reducing the burden of malaria. There has been much skepticism and some confusion about this, (including in this journal; see ref. 11 and *Letters,* p. 234) with some people implying that malaria transmission rates must be reduced to zero to remove malaria from a particular environment. The same confusion has led many malaria experts to reject Ronald Ross' (correct) claim[12] that below a certain transmission rate, that of a basic reproduction number[10] equal to 1, malaria cannot be sustained. Such perceptions, that malaria TBVs would have little effect, have fed the lack of commercial interest in their development. The meeting gave in-depth consideration to the potential effect of TBVs and reached the following main conclusions.

In most malaria-endemic locations, TBV coverage, even if partial, would reduce disease and death due to malaria. In areas of relatively low transmission, as in most endemic locations outside tropical Africa, and also possibly in parts of tropical Africa itself, malarial disease would be reduced probably in direct proportion to the effective coverage with TBVs. In many situations of low malaria endemicity, transmission could be stopped by TBVs. In some more highly endemic areas, the deployment of TBVs in conjunction with more traditional measures such as insecticide-impregnated bed nets could bring the end of malaria transmission within reach. Even incomplete TBV coverage would slow the build-up of malaria epidemics and reduce their size very substantially in many situations[13].

Because of the limited dispersal range of the mosquito vectors of malaria (a few hundred meters to a kilometer), individual communities composed of stable and settled human

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populations could probably be protected from malaria by small, local TBV vaccination campaigns. The idea that a TBV program requires the vaccination of individuals who will not themselves benefit has often been raised as an ethical objection to TBVs. However, for the same reason that the vectors of malaria have limited dispersal, it follows that within a vaccinated household the household members themselves, usually members of the same family, and their immediate neighbors will tend to be the main beneficiaries of such vaccination. The ethical nature of TBV in this context was a view endorsed by representatives from the endemic countries.

One further important property of TBVs is that they would reduce the emergence and spread of parasites resistant to other malaria vaccine components, and even to anti-malarial drugs. In this respect, the use of TBVs could substantially prolong the effective life of other malaria vaccine components and possibly also of anti-malarial drugs.

At the technical level, much progress has been made in identifying suitable target antigens for TBV against both of the main species of human malaria, *P. falciparum* and *P. vivax* (Table 1 & 2). These antigens are surface proteins of the extracellular sexual stages of the parasites—gametes and zygotes—in the midgut of a blood-fed mosquito[9] (Fig. 1*c*). Moreover, the immune mechanism of transmission-blocking immunity against these antigens is known (antibody-mediated blockade of the development of the parasites in the mosquito). This has enabled an *ex vivo* assay (gametocyte-infected blood fed to mosquitoes through an artificial membrane in the presence of serum from an immunized subject) to be used as a realistic test for malaria transmission-blocking immunity. Using this assay, the immunogenicity of a TBV construct can be tested in human volunteers without requiring the infection of each volunteer with malaria. This is an enormous advantage in the development of a human vaccine. Immunogenic constructs representing zygote surface antigens of both the main human malaria parasites *P. falciparum* and *P. vivax* have been produced in yeast and have passed through the early stages of TBV trials using the assay described above.

A problem specifically associated with the current leading candidate antigens for TBVs is that they will probably not be boosted by malarial infection (Table 1 & 2). This is because these antigens, the Pfs25 and Pfs28 zygote surface proteins of *P. falciparum* (and their equivalents for *P. vivax*), are expressed only after fertilization in the mosquito midgut and are not present in the gametocytes as they circulate in the blood. Thus, a vaccinated community could be at risk of an epidemic return of malaria once their vaccine-induced transmission-blocking immunity has waned. Therefore, formulations may need to be developed to extend the effective life of TBV-induced immunity.

Difficulties in the deployment of TBVs are likely to arise in achieving optimum levels of coverage, as adults as well as infants and children will need to be vaccinated. There would be a real challenge in explaining the concept of a vaccine that prevents the spread of infection without conferring direct protection upon the individual. It is to be hoped, however, that the transmission-blocking components of a malaria vaccine would be used in formulations that included components for the direct protection of the vaccinated individual against malarial infection. In any event, malaria vaccination campaigns will have to be part of an integrated program of malaria control in which educational, health and vector-control services work together. In this context, most of the difficulties described here could be overcome.

Therefore, the consensus of the meeting was that TBVs

**Table 2** Properties and current state of product development of leading malaria transmission-blocking vaccine candidates

| Antigen | Strengths | Weaknesses | Current State of Development |
|---|---|---|---|
| Pfs48/45 | Antibodies to Pfs48/45 can completely block transmission of *P. falciparum* to mosquitoes.<br><br>Expressed on the gametocyte during the infection in the human host; probable boosting of transmission-blocking antibody response during an infection.<br><br>Essential for fertilization in gene knock-out experiments. | Difficulty in expressing recombinant products in immunogenic form. | *P. falciparum* gene cloned.<br><br>Protein expressed in *E. coli* does not induce transmission-blocking activity. |
| Pfs230 | Antibodies to Pfs230 can completely block transmission of *P. falciparum* to mosquitoes.<br><br>Expressed on the gametocyte during the infection in the human host; probable boosting of transmission-blocking antibody response during an infection. | Very large molecule; difficult to determine which regions would be effective in a vaccine. | *P. falciparum* gene cloned.<br><br>Fragments have been expressed as *E. coli* MBP-fusion proteins; induce some transmission-blocking activity.<br><br>Fragments have been expressed in yeast; induce some transmission-blocking activity. |

would be very valuable tools against malaria and that their production is technically feasible. Moreover, the effects of a TBV would be complementary and even synergistic in combination with other malaria vaccine components and control measures.

Given the present lack of industrial interest in a malaria TBV, the problem remains of how to fund and manage the large-scale developmental research and the human trials of candidate TBVs. The situation calls for a substantial public sector intervention. In response to this, the Bethesda meeting proposed the formation of a consortium of interested parties and a secretariat to plan and manage the development of a malaria TBVs. Its mission would include the coordination of TBV research and development, the mobilization of funds for these operations, and negotiations with other organizations, such as governments of countries where trials would take place, whose involvement would be necessary to reach the goal.

Thus, scientists from laboratories around the world have declared an interest and a commitment to the development of malaria TBVs and have proposed a mechanism through which this might be achieved. The question now is: Who will support and finance such a venture?


1. *The World Health Report: Making a difference*. (World Health Organization, Geneva, 1999).
2. Sinton, J.A. What malaria costs India, nationally, socially and economically. *Records Malaria Surv. India* **5**, 223–264, 413–489 (1935)
3. Sinton, J.A. What malaria costs India, nationally, socially and economically. *Records Malaria Surv. India* **6**, 91–169 (1936)
4. *Resolving the DDT dilemma*. (WWF Canada and WWF US, June, 1998).
5. Roberts, D.R., Laughlin, L.L., Hsheih,P. & Legters,L.J. DDT, Global Strategies, and a Malaria Control Crisis in South America. *Emerg. Infect. Dis.* **3**, 295–302 (1997)
6. Saul, A. Towards a malaria vaccine: riding the roller-coaster between unrealistic optimism and lethal pessimism. *Southeast Asian J. Trop. Med. Public Health* **23**, 656–671 (1992)
7. Engers, H.D. & Godal, T. Malaria vaccine development: current status. *Parasitol. Today* **14**, 56-54 (1998)
8. Holder, A.A. Malaria vaccines. *Proc. Natl Acad. Sci. USA* **96**, 1167–1169 (1999)
9. Kaslow, D.C. Transmission-blocking vaccines: uses and current status of development. *Int. J. Parasitol.* **27**,183–189 (1997)
10. Malaria transmission blocking vaccines: An ideal public good. *WHO document no. (TDR/RBM/MAL/VAC/2000.1)* available from WHO Geneva and on websites http:\\www.who.int\tdr and http:\\mim.nih.gov
11. Birmingham, K. EC panel decisions surprise malaria community. *Nature Med.* **5**, 1333–1334 (1999)
12. Ross, R. *The Prevention of Malaria*. (John Murray, London, 1911).
13. Saul, A. Minimal efficacy requirements for malarial vaccines to significantly lower transmission in epidemic or seasonal malaria. *Acta Trop.* **52**, 283–296(1993)



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